REMARKS

Claims 1, 6-8, 12, 15, 16, and 21 have been amended. Claims 1 and 16 have been amended to specify that the double-stranded DNA nucleotide sequence of between about 50 and about 250 bases comprises the spacer that is not present in the cell. Support for the amendments can be found in the Specification as filed, for example, on page 20, line 23 through page 21, line 11 (Example 1). In this example, a double-stranded spacer sequence from CMV (i.e. a viral sequence) is linked to probes containing binding sites for NFkB, CREB, and AP-1 (i.e. cellular transcription factors). Therefore, the spacer sequence is not present in the biological sample that naturally has the NFkB, CREB, and AP-1 transcription factors. Claim 20 has been cancelled without prejudice. No new matter has been introduced by these amendments. The following addresses the substance of the Office Action.

Compliance with 35 USC §112

The Examiner has rejected Claims 6-8, 12, 15 and 21 under 35 USC §112, second paragraph as being indefinite. More specifically, Claims 6-8 were found indefinite for reciting an intended use for the method of claim 1. Claims 6-8 have been amended accordingly.

Claim 12 was found indefinite for having insufficient antecedent basis for the phrases "the insoluble solid support". Claim 12 has been amended to now recite "the solid support".

Claim 15 was found indefinite for reciting the phrase "wherein the double-stranded DNA sequences fixed on the support surface contain in part or totally one or several of the specific DNA sequences presented in the table 1". Claim 15 has now been amended to recite "wherein the double-stranded DNA sequences fixed on the support surface contain one or several of the specific DNA sequences presented in the table 1".

Claim 21 was found indefinite for reciting the phrase "step of identifying transcriptional factors". Claim 21 has now been amended to recite "step of identifying activated transcriptional factors and/or peptides which are part of the activated transcriptional factor(s) complex".

Applicant has addressed all the rejections under 35 USC §112, second paragraph of Claims 6-8, 12, 15 and 21, which are now definite. Therefore, their rejection should be withdrawn.

Non-obviousness

The Examiner has maintained the rejection of Claims 1, 2, 4-8, 12-19, 21, 22, 36, 37, 39 and 40 under 35 USC §103(a) as being allegedly unpatentable over Peterson et al. (US 5,563,036) in view Brand et al. (*J. Clin. Invest.* 1996, 97:1715-1722), Heslot et al. (US 6,342,353) and Nerenberg et al. (US 2002/0015198). Specifically, the Examiner has maintained that it would have been obvious at the time the invention was made to a person with an ordinary skill in the art to modify the teachings of Peterson et al. with that of Brand et al., Heslot et al. and Nerenberg et al. to arrive at the claimed invention.

As discussed in the Inventor's Declaration filed herewith under 37 C.F.R §1.132, the inventors discovered a mechanism for assessing the activation state of transcriptional factors in a biological sample. The inventors tested the effects of the presence or absence of a spacer separating the specific binding site for the transcription factors from the solid support, as well as the length and the composition of the spacer on the final combination of high specificity and high sensitivity of the method. The inventors showed that when activated transcription factors are contacted with short double-stranded DNA sequences without a spacer, the assay is quite specific but not at all sensitive (i.e. giving false negative results). When activated transcription factors are contacted with long double-stranded DNA sequences without a spacer, the assay is sensitive but not specific (i.e. giving false positive results).

However, Applicants unexpectedly discovered that activated transcription factors present in very low amounts in a cell or cell lysate can be assayed in a binding assay combining double-stranded DNA sequences comprising the binding sites for the activated transcription factors and a spacer comprising a double-stranded DNA nucleotide sequence of between about 50 and about 250 base pairs, said nucleotide sequence being not present in the tested cell (see paragraph 8). When such constrained specifications are met, the assay becomes both sensitive enough to assay biological samples and specific (suppressing both the false negative and false positive results) even when a plurality of transcription factors is simultaneously assayed on a micro-array. Furthermore, the kinetics of the binding is sufficient to permit obtaining results in a very short time frame.

Thus, the data presented in the Declaration unambiguously show that the method as claimed is sensitive and specific (see paragraph 9), when the conditions are as follows: low

amounts of activated transcription factors are contacted with double-stranded DNA sequences having a short specific binding site for the transcription factors, separated from the support by a spacer containing at least a double-stranded nucleotide sequence of between about 50 and about 250 base pairs, which is not present in the cell containing the transcription factors to assay.

The high sensitivity obtained with the present method allows the use of non radioactive detection means, and provides advantages over the method of Peterson et al.: a non radioactive detection method avoids the drawbacks linked to the use of radioactive labels; quantification of the activated transcription factors is possible because the signals obtained reflect the binding of the activated transcription factors to their specific binding sequence only, and not to the spacer nucleotide sequence; and the method allows the detection of very small amounts of activated transcription factors among huge amounts of other proteins, which is a hallmark of cell-derived samples.

Peterson et al. describe double-stranded DNA sequences having at least a portion of nucleotide sequence naturally involved in the regulation of the transcription of the gene which is necessary for sequence-specific interaction with the transcription factor. Peterson et al. do not teach that the double-stranded DNA is connected to the surface of the solid support by a spacer comprising at least a double-stranded DNA nucleotide sequence of between about 50 and about 250 base pairs. Furthermore, Peterson et al. neither suggest nor mention the use of a spacer which is a nucleotide sequence that is not present in the cell containing the activated transcription factors to assay.

Heslot et al. provide methods for characterizing nucleic acid duplexes by recording a signature of said duplexes which is linked to the force variation required for separating and repairing the two sequences . Heslot et al. disclose a method involving the immobilization of double-stranded DNA via a spacer arm which is also double-stranded DNA, wherein said spacer arm is at least 100 bases in length but preferably corresponds to 1 kb or even comprises from 5 to 100 kb (column 4, lines 36-39). Heslot teaches that the freedom of movement of the double-stranded DNA increases with the length of the spacer arm.

This feature is incompatible with the present assay since long spacer sequences would bind multiple transcription factors giving false positive results. As provided by the literature, non protected regulatory regions of a gene may be the targets of many transcription factors (Yang

et al. (2007) *Annals of Biomedical Engineering*, 35(6):1053-1067, attached) which may interfere with the assay.

In the example provided by Heslot (column 10, lines 49-50), the spacer arm (DNA2) is a lambda phage DNA which is from the same organism as the lambda phage DNA intended to be opened (DNA1). In the present invention, there is a limitation on the spacer sequence, which is not a nucleotide sequence present in the target cell.

Therefore, currently amended Claims 1, 2, 4-8, 12-19, 21, 22, 36, 37, 39 and 40 are not obvious of the cited references, and their rejection under 35 USC §(a) should be withdrawn.

The Examiner has maintained the rejection of Claim 34 under 35 USC §103(a) as being allegedly unpatentable over Peterson et al. (US 5,563,036) in view of Brand et al. (*J. Clin. Invest.* 1996, 97:1715-1722), Heslot et al. (US 6,342,353) and Nerenberg et al. (US 2002/0015198), and further in view of Dattagupta et al. (US 4,968,602).

Claim 34 depends from Claim 12, which depends from Claim 1, which is asserted to be non obvious over Peterson et al. in view of Heslot et al. and Nerenberg et al. Dattagupta fails to cure the deficiencies of these references. Therefore, Claim 34 is also non-obvious over the cited references, and its rejection under 35 USC §103(a) should also be withdrawn.

Double Patenting

The Patent Office has maintained the rejection of claims 1, 2, 4-8, 12-18, 22, 34, 36 and 37 and rejected claims 39 and 40 on the grounds of obviousness-type double patenting over claims 1-21, 25 and 26 of copending Application No. 10/821,568. A terminal disclaimer may be used to overcome an obviousness-type double patenting rejection. Applicant will defer filing a terminal disclaimer until the rejected claims are otherwise indicated to be in condition for allowance.

CONCLUSION

Applicants have endeavored to address all of the Examiner's concerns as expressed in the outstanding Office Action. Accordingly, amendments to the claims, the reasons therefor, and arguments in support of the patentability of the pending claim set are presented above. In light of the above amendments and remarks, reconsideration and withdrawal of the outstanding rejections is specifically requested. If the Examiner finds any remaining impediment to the prompt allowance of these claims that could be clarified with a telephone conference, the Examiner is respectfully requested to initiate the same with the undersigned.

Please charge any additional fees, including any fees for additional extension of time, or credit overpayment to Deposit Account No. 11-1410.

Respectfully submitted,

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